

Egyptian Herbal Monograph

Volume 1

Wild Medicinal Plants

Egyptian Drug Authority (EDA)

2026



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Citrullus colocynthis L.

حنظل – حنضل

1. Names & Synonyms (1-3)

Citrullus colocynthis L.

Family: Cucurbitaceae.

Syns. *Cucumis colocynthis*

Colocynthis vulgaris.

Arabic: Hanzal حنظل - Handal حنضل.

English: Colocynth, Bitter apple, Bitter gourd.

2. Geographical distribution

Common in nearly all the phytogeographical regions of the country (3).

3. Parts used for medicinal purpose

Colocynth; Pulp of the peeled fruit (dried unripe, but fully grown fruit deprived of its seeds and hard outer part of pericarp) (4, 5); seeds, leaves, and roots are also used (2, 6).

4. Major chemical constituents (3)

- **Cucurbitacins and its glycosides** (7): Cucurbitacin A, B, C, D, E, I, J, K and L (8-13), 2-O- β -D-glucopyranosyl-cucurbitacin I, 2-O- β -D-glucopyranosyl-cucurbitacin L (14), colocynthein, colocynthetin (15), and Cucurbitane-type triterpenoid glycoside (saponin) (16) as colocynthosides A and B (11) are major constituents in the fruit.
- **Flavonoids:** Quercetin (leaf, stem, fruit, root), flavone-C-glucoside (Isovitexin), isoorientin and isoorientin 3'-O-methylether (fruit), C-*p*-hydroxybenzyl derivatives as 8-C-*p*-hydroxybenzylisovitexin, 6-C-*p*-hydroxybenzylvitexin, 8-C-*p*-hydroxybenzylisovitexin 4'-O-glucoside (aerial parts) (14, 17,18), kaempferol (19), catechin, myricetin (19-21), isoscoparin and isosaponarin (14).

- **Phenolic acids:** Gallic (20), *p*-hydroxybenzoic, chlorogenic, caffeic, vanillic acid, *p*-coumaric, sinapic and ferulic acids from fruit pulp (19), and 3-O-caffeoylquinic acid from the leaves (22).
- **Alkaloids:** Alkaloids from the whole fruit and pulp (13, 23- 26); choline from fruit pulp (24), 2-(nonan-8-one) -(1H)-4-quinolone and 2-(nonan-8-one) 4-methoxy-quinoline from the aerial parts (27).
- **Fatty acids:** Linoleic, oleic, palmitic, stearic, myristic, linolenic (17, 28-31) and arachidic acids from seeds (20).
- **Amino acids:** Arginine (in pulp), aspartic acid (in rind) and glutamic acid (in seeds) (32).
- **Others:** (17)
 - Protein: rich in lysine, leucine, sulfo-amino acids as methionine.
 - Vitamins: Vitamin B (Thiamine, Riboflavin and Niacin).
 - Minerals: Ca, Mg, Mn, K, P, Fe and Zn .
 - Tocopherols and Carotenes: α -Tocopherol (20), γ -tocopherol and β -carotene from fruit seed oil (33).
 - Volatile compounds (fruit pulp): 2-Methyl, 4-heptanone, 3-methyl, 2-heptanone, trimethylsilyl methanol and 1-propoxy pentane (34).

5. Medicinal uses

A. Well-established

Oral: Purgative (4-5).

B. Traditional use

Externally: Rheumatic disease (low back, knee and joints pain) (35-37).

C. colocynthis is a traditional medicinal plant for use in the specified indications exclusively based upon long-standing use.

6. Herbal preparations correlated to medicinal use

1. Oral dried fruits powder (4-5).
2. Topical Poultice (with warm cooking oils) (35-37).

7. Posology and method of administration correlated to medicinal use

Preparation 1

Indication A

Oral: 0.1 – 0.3g of dried fruits powder as purgative (4-5).

Preparation 2**Indication B**

Externally: Poultice is made of colocynth with warm cooking oils to place it topically on the joint for rheumatic pain (35-37).

Method of administration: Oral and external use.

8. Contraindications

Hypersensitivity to active substances and to other plants of the same family.

9. Special warnings and precautions for use

- Colocynth should be used under medical supervision and in proper dose as it is severely poisonous. It has a strongly irritating and painful effect on mucous membranes due to its content of cucurbitacin glycosides, out of which cucurbitacins are released in watery environments (38).
- **Diabetes:** Colocynth might lower blood sugar levels. Blood glucose levels should be regularly monitored in diabetics (39).
- **Surgery:** Colocynth might interfere with blood sugar control during and after surgery. Colocynth should be stopped at least 2 weeks before a scheduled surgery (39).
- Encouraging use of seeds (containing no saponin) instead of the whole fruit or pulp (40).

10. Interactions with other medicinal products and other forms of interaction (39)**- Digoxin**

Colocynth is a stimulant laxative which can decrease potassium levels in the body therefore can increase the risk of side effects of digoxin.

- Warfarin

Colocynth can work as a laxative. In some people colocynth can cause diarrhea which can increase the effects of warfarin and increase the risk of bleeding.

- Diuretic drugs

Colocynth is a laxative agent and can decrease potassium in the body. Diuretic drugs can also decrease potassium in the body. Accordingly, concomitant use with diuretic drugs might severely decrease potassium in the body. Some diuretic drugs that can decrease potassium include chlorothiazide, chlorthalidone, furosemide, hydrochlorothiazide, and others.

11. Fertility, pregnancy and lactation

Colocynth is not recommended in pregnancy and breast-feeding (39) <<see section 15; Relevant biological activities>>.

Long term exposure to *C. colocynthis* L. may cause adverse effects on the reproductive system and fertility (41) <<see section 15; Relevant biological activities >>.

12. Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

13. Undesirable effects

- If adverse reactions occur, a doctor or a pharmacist should be consulted.
- Gastrointestinal disorders such as diarrhea, painful cramp (42), colitis (43, 44); intestinal damage (45); the dried fruit pulp is irritating to the eye and powdered colocynth pulp causes severe pain if it meets the nasal mucous membrane (46-47); leucocytosis (48-49).

14. Overdose

- Vomiting, bloody diarrhea, colic, and kidney irritation following the intake of toxic dosages (0.6 to 1 g), and then increased diuresis that progresses to anuria. Lethal dosages (starting at 2 g) lead to convulsions, paralysis and, if untreated, lead to death through circulatory collapse. The treatment of poisonings should proceed symptomatically following gastric lavage (38).
- In case of poisoning, a dilute tannic acid solution should be taken, followed by large quantities of drinks that contain eggs (albuminous drinks) (39).

15. Relevant biological activities

Analgesic, anti-inflammatory and antinociceptive

- Carrageenan-induced edema in a rat hind paw was carried out to evaluate the topical anti-inflammatory effect of the *C. colocynthis* (CC) fruit extract cream (2–8%) and the tissue levels of IL-6 and TNF- α were estimated by using a commercial ELISA kit. Also the topical antinociceptive activity of the CC cream (2–8%) was evaluated in rat formalin test. The study indicated that topical application of CC cream possesses significant anti-inflammatory and antinociceptive activities in animal models, which were probably mediated by opioid receptors and the suppression of pro-inflammatory cytokines (TNF- α and IL-6) (50).

- *C. colocynthis* aqueous extracts of the plant different parts were screened for analgesic and anti-inflammatory activities using the acetic acid writhing test in mice and the carrageenan-induced paw edema assay in rats, respectively. All extracts displayed analgesic and anti-inflammatory activities at different doses without inducing acute toxicity. The best results were obtained with immature fruits followed by seeds. The stem and root extracts were shown to possess the less significant inhibitory activity against the analgesic and anti-inflammatory models used (51). Also, the same assessment was carried out on the immature fruit and seeds organic extracts (petroleum ether, chloroform, ethyl acetate, acetone and finely methanol extract). All extracts displayed an important analgesic and anti-inflammatory activities at different doses without inducing any side effects. Experiment results provide scientific insight into the ancient practice of utilizing *CC* as analgesic and as anti-inflammatory agents (52).
- The extract of the dried pulp of the plant fruits was studied for its effects through inhibition of inflammatory cytokines secreted in obesity conditions on male mice. The fed animals received 50 mg/kg of hydroalcoholic extract by gavage for 42 days. TNF- α , IL-6 and IL-10 in serum were assayed by ELISA technique after every two weeks. The extract dramatically decreased expression of TNF- α 44.83 (** $p < 0.001$), IL-6 30.23 (** $p < 0.001$) and marginally increased IL-10 5.31 (ns- $p > 0.05$) in obese mice. This study demonstrated that, although the extract did not show anti-obesity effects, it could have an anti-inflammatory effect through down regulation of obesity-associated pro-inflammatory cytokines (53).
- The effect of ethanol extract of the roots at dose of 20 ng/ml on inflammatory cytokine expression in inflamed cells with LPS20 both cartilage cells/macrophage was examined. The results indicated that the ethanol extract of root can reduce expression levels of pro-inflammatory cytokines in inflamed cells caused by situation same as that of osteoarthritis (54).
- Sodium carboxymethyl cellulose (5%) topical gel formulations containing 3% of *Colocynth* extract, hydrolyzed extract, or acetylated extract were studied for their release through cellophane membrane and their permeability through hairless mouse skin and, for the *in vivo* anti-inflammatory activity of the different types of *colocynth* extract using the carrageenan induced paw edema model in albino rats in comparison with the commercial Voltarin Emulgel®. The acetylated extract gel showed comparatively rapid permeability through hairless mouse skin, with low release rate through cellophane membrane. The pharmacological screening revealed that the percent reduction of edema produced by *colocynth* extract was 45.39%, the hydrolyzed extract produced 54.11% inhibition and the acetylated extract produced 64.95%, while Voltarin Emulgel® produced 63.35%. This means that acetylated *colocynth* extract can be used as an effective local anti-inflammatory agent (55).

- Fruit extracts in methanol were subjected to check anti-inflammatory activity against carrageenan induced paw edema, serotonin induced edema and prostaglandin E1-induced paw edema in albino rats. Extracts showed anti-inflammatory activity against all types of edema but the most significant results were seen against prostaglandin E1-induced paw edema (56).

Toxicity

- The study was undertaken to determine the acute median lethal dose of the methanol extract of the fruit of *C. colocynthis* and to evaluate the toxic effects of this extract at a single daily oral dose (131mg/kg) in 50 Albino rats. Liver, kidney and bone marrow function test were assessed using standard techniques. The acute median lethal dose of the extract was found to be 1311.45 mg/kg. The plasma ALT, AST, urea, and creatinine levels were significantly affected, an indication that the extract is hepatonephrotoxic. The results obtained for hematological parameters reflect that methanol extract at a dose of 131 mg/kg did not affect quantitatively but disrupted qualitatively some functions of the bone marrow. The study also showed that the intake of extract of ripe *C. colocynthis* fruit presented some adverse effects on the functions of the liver, kidney, and bone marrow in rats (57).

- The toxic effects of *C. colocynthis* on male rabbits were investigated. Test animals were treated with 100 or 200 mg/kg/day of either pulp or seed extract. One month later, surviving animals were sacrificed and specimens of small intestine, kidney, and liver were prepared for morphological evaluation. No animals treated with 200 mg/kg/day of pulp extract survived. Animals treated with 100 mg/kg/day of pulp extract displayed sever lesions in the small intestine, kidney, and liver. Interestingly, animals treated with either 100 or 200 mg/kg/day of seed extract displayed only minor intestinal insult. In contrast to seeds extract, pulp extract of *C. colocynthis* can be fatal to rabbits. Therefore, seeds extract may be the preferred route for therapeutic application (45).

- The toxic effect of alcoholic extract of *C. colocynthis* on rat Liver was investigated with a single daily dose of (50, 100, 200, 400 g/kg) administered intraperitoneally. The results indicated that there is a morphological change in liver cells including karyrrhexis, chromatolysis, and granulation of the cytoplasm. Additionally, collagen and reticular fibers were evident in liver parenchyma in high doses. *C. colocynthis* can have toxic effects on liver cells which may induce hepatocyte necrosis and liver fibrosis. These effects were dose dependent (58).

- The acute toxicity studies of the methanolic extract of dried fruit pulp of *C. colocynthis* (Cucurbitaceae) in albino mice NMRI indicated the highly toxic nature of the colocynth. A very significant decrease in body weight of test animals was noted at $p < 0.05$. The LD₅₀ was calculated as 1000mg/kg body weight. Within four days of experimentation, mortality was 100%. Histopathological studies confirmed the toxic

nature of extract. Gross changes in histology of heart, liver and kidneys were noted. Section of spleen did not exhibit any abnormality (59).

- Ethanolic extract of the plant fruits was investigated for its sub-chronic toxicity on Sprague Dawley (SD) rats, to develop safe doses, 30 male rats were used with 0, 12.5 and 25 mg/kg of the extract twice per week for 8 weeks. The raw extract of the fruits at dose of 12.5 mg and 25 mg/kg induced significant increase in level of creatinine and total protein and increased non-significantly levels of glucose and blood urea while reduced level of triglycerides, total cholesterol, and high-density lipoprotein-cholesterol significantly when compared with control group. Histopathological examination revealed that kidney of rat treated with *C. colocynthis* at dose of 12.5 mg/kg show interstitial chronic inflammatory cell infiltrate while kidney of SD-rat treated with *C. colocynthis* at dose of 25 mg/kg showed interstitial fibrosis stained with Mallory trichrome stain. While liver showed lytic necrosis replaced by leukocyte infiltration at dose of 12.5 mg/kg of raw extract and rat treated with 25 mg/kg show interstitial fibrosis stained with Mallory trichrome stain. Raw extract of the fruits had adverse effect on liver and kidney while in improving lipid profile and hematology in a novel manner in SD rats at selected dosed (60).

Case Presentations

- Four patients with colocynth intoxication are presented. The main clinical feature was acute rectorrhagia preceded by mucosal diarrhea with tenesmus, which gradually progressed to bloody diarrhea and overt rectorrhagia within 3 to 4 hours. The only colonoscopic observation was mucosal erosion which was completely resolved in follow-up colonoscopy after 14 days.

The membranolytic activity of some *C. colocynthis* ingredients is responsible for the intestinal damage. Patients and herbalists should be acquainted with the proper use and side effects of the herb. Clinicians should also be aware of *C. colocynthis* as a probable cause of lower GI bleeding in patients with no other suggestive history, especially diabetics (40).

- Three examples were reported of toxic acute colitis which occurred after ingestion of *C. colocynthis* for ritual purposes. The prominent clinical feature was dysenteric diarrhea; colonoscopic changes included congestion and hyperaemia of the mucosa with abundant exudates but no ulceration or pseudopolyp formation. A causal relationship between colonic injury and the intake of colocynth was supported by the following features: (1) the pharmacology of the colocynth extract ingested; (2) the temporal relationship between colocynth intake and clinical onset (eight to 12 h); (3) the rapid recovery within three to six days, with normal endoscopy at day 14; (4) the absence of other possible causes for the observed patterns, except in one case, in which a concomitant intestinal infection with *Clostridium perfringens* Type A was discovered; (5) the specific pathological features. Colonic biopsies taken 27, 44, and 72

h after colocynth intake showed: erosions with fibrino-purulent exudate, early fibrosis of the lamina propria, hyaline thickening of the superficial epithelial basal membrane. These pathological features completely disappeared within 14 days in all three cases (61).

Pregnancy and Lactation

In Ayurvedic medicine, the fruit pulp has a reputation of causing miscarriage, when administered to pregnant women (62) and colocynth has also been used for this purpose in Europe (49, 63). Such activity could arise indirectly from congestion in the pelvic region as a manifestation of the cathartic action (62). It should be added, however, that on several occasions colocynth was ineffective as an abortive agent, even though it produced serious poisoning (63).

Fertility

- An ethanolic extract of *C. colocynthis* seeds, administered at an oral dose of 200 mg/kg for 2 days, did not inhibit copper acetate induced ovulation in rabbits to such an extent that further research seemed warranted (64). Different extracts of *C. colocynthis* were screened for anti-implantation activity by feeding female rats with each extract from day 1 to day 7 of their pregnancy. Acetone and methanolic root extracts in doses of 150 mg/kg prevented implantation in 3 and 4 of 7 test animals, respectively, whereas 200 mg/kg of an ethanolic leaf extract and 150 mg/kg of a benzene leaf extract inhibited implantation in 4 of 6 rats (65). The spermatotoxicity was observed in mice treated with an alcoholic extract of *C. colocynthis* fruit in daily oral doses of 0.1 g/kg body weight for 3 months (48). Early textbooks claim that *C. colocynthis* is excreted into breast milk and should therefore not be given to nursing women (66-68).

The short and long effects of *C. colocynthis* L. (400 mg/kg/body weight) on the reproductive system after administration to female Sprague-Dawley rats were investigated. The rats were intraperitoneally injected in dose of 400 mg/kg/body weight. First group received treatment for 4 weeks and a second group received the same dose of treatment for a period of 12 weeks. Female rats were allowed mating with males after 10 days prior to the last administration dose. Several parameters were determined including: number of pregnant rats, body and reproductive organ weight, number of implantation sites, viable fetuses and resorption sites. The results indicate that long-term exposure of female rats to *C. colocynthis* L. causes adverse effects on the reproductive system and fertility (41).

16. Additional Information

Colocynth has a drastic purgative and irritant action and has been superseded by less toxic laxatives. It is used in homoeopathic medicine (69).

C. colocynthis has showed wide range of pharmacological activities including:

- Antidiabetic, hypoglycemic and antihyperglycaemic activities (30, 70-85).
- Peripheral neuropathy (86).
- Antioxidant activity (19, 87-90).
- Hair growth effect (91, 92).
- Anti-microbial activity (13, 25, 93-98).
- Anthelmintic activity (99-103).
- Cytotoxic activity (87, 104-106).
- Hypolipidemic effect /antihyperlipidemic (89, 107,108).
- Hepatoprotective effect (109-111).

17. Date of compilation/last revision

30/8/2023.

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